General

Guideline Title

Stem cell transplantation in the treatment of acute lymphoblastic leukemia.

Bibliographic Source(s)

Bredeson C, Varela NP, Walker I, Kuruvilla J, Kouroukis CT, Stem Cell Transplant Steering Committee. Stem cell transplantation in the treatment of acute lymphoblastic leukemia. Toronto (ON): Cancer Care Ontario (CCO); 2016 Feb 1. 37 p. (Program in Evidence-based Care (PEBC) Recommendation Report; no. SCT-6). [32 references]

Guideline Status

This is the current release of the guideline.

The Recommendation Report over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario (CCO) Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Recommendation 1

Allogeneic stem cell transplantation (allo-SCT) is an option for adult patients with acute lymphoblastic leukemia (ALL) in first complete remission (CR1). Allo-SCT is recommended in second complete remission (CR2) or greater (refractory or relapsed).

Recommendation 2

A myeloablative conditioning is the conventional regimen for most patients with leukemia; however, reduced-intensity conditioning (RIC) is an option for patients with ALL in remission when they are deemed unsuitable for the standard myeloablative conditioning (MAC) regimen.

Recommendation 3

Post-transplant use of a BCR-ABL tyrosine-kinase inhibitor (TKI) in patients with Philadelphia chromosome-positive ALL is a reasonable option.

Recommendation 4

Haploidentical hematopoietic stem cell transplantation (haplo-SCT) for patients with ALL in CR1 or later who lack a suitable related or unrelated

donor is a reasonable option.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Acute lymphoblastic leukemia (ALL)

Guideline Category

Management

Treatment

Clinical Specialty

Hematology

Oncology

Intended Users

Advanced Practice Nurses

Hospitals

Patients

Physician Assistants

Physicians

Guideline Objective(s)

- To establish the indications for allogeneic stem cell transplantation (allo-SCT) in the management of acute lymphoblastic leukemia (ALL) in adults
- To identify the role of reduced-intensity conditioning (RIC) regimens for SCT in the management of ALL of adult patients
- To identify the role of tyrosine-kinase inhibitors (TKIs) for patients undergoing allo-SCT for Philadelphia chromosome-positive ALL
- To identify the role of alternative donor transplantation (haploidentical, cord blood) in the management of adult patients with ALL who lack a suitable related or unrelated donor
- To summarize the available evidence and to standardize practice in Ontario amongst all SCT centres and to assist referring physicians in knowing which patients with ALL might be best suited for an SCT

Target Population

All adult acute lymphoblastic leukemia (ALL) patients considered for treatment that involves stem cell transplantation (SCT)

Interventions and Practices Considered

1. Allogeneic stem cell transplantation (allo-SCT)
2. Standard myeloablative conditioning
3. Reduced-intensity conditioning (RIC)
4. Post-transplant use of a BCR-ABL tyrosine-kinase inhibitor (TKI) in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL)
5. Haploidentical hematopoietic stem cell transplantation (haplo-SCT)

Major Outcomes Considered

- Relapse rate
- Disease-free survival
- Relapse-free survival
- Progression-free survival
- Overall survival
- Non-relapse mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Given the availability of the high quality 2012 American Society for Blood and Marrow Transplantation (ASBMT) guideline presented and described in Section 2 of the original guideline document, this evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described below.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. The Web site of the Cochrane Database of Systematic Reviews (CDSR) (www.cochrane.org/evidence), along with the electronic databases MEDLINE (OVID) and EMBASE (OVID) were searched from January 2008 to July 2014 (and updated in May 2015). The full literature search strategy used to identify potentially relevant systematic reviews from OVID MEDLINE and EMBASE is presented in Appendix 3 of the original guideline document. The Web site of the CDSR was searched using the keyword "Acute Lymphoblastic Leukemia".

Systematic reviews were included if:

1. The existing systematic review searched for studies evaluating any of the following indications in the management of acute lymphoblastic leukemia (ALL): allogeneic stem cell transplantation (allo-SCT), reduced-intensity conditioning (RIC) regimens for allo-SCT, tyrosine-kinase inhibitor (TKIs) following allo-SCT, and alternative donor transplants in the management patients who lack a suitable related or unrelated donor.
2. The literature search strategy for the existing systematic review is reproducible (i.e., reported) and appropriate.
3. The existing systematic review reported the sources searched as well as the dates that were searched.

Identified systematic reviews were evaluated based on their clinical content and relevance. Any identified systematic reviews that addressed the research questions were assessed using a Measurement Tool to Assess Systematic Reviews (AMSTAR). The results of the AMSTAR assessment were used to determine whether or not any existing systematic review could be incorporated as part of the evidence base. In cases where multiple systematic reviews of similar quality exist, only the most recent review with the most recent literature search would be included.

Search for Primary Literature

Assuming that no existing guidelines or systematic reviews were identified, or that identified guidelines or systematic reviews were incomplete in some fashion, a systematic review of the primary literature was also planned. If a suitable guideline or systematic review were found, a systematic review of the primary literature would be conducted, from the end date of the reported search, only to update the evidence from the identified guideline(s) and/or systematic review(s).

Literature Search Strategy

The MEDLINE (OVID) (1996 through July 18, 2014) and EMBASE (OVID) (1996 through week 30, 2014) databases were searched for evidence on July 2014 and updated on May 2015. The search strategy included a logical combination of terms for the condition (ALL), the intervention (SCT), and studies of interest (systematic reviews, clinical trials, non-randomized studies with an appropriate control group). The full literature strategy used to retrieve potential relevant studies is presented in Appendix 3 of the original guideline document.

Study Selection Criteria and Process

Inclusion Criteria

Articles identified in this systematic review were eligible for inclusion if they met the following criteria:

> Primary comparative studies evaluating any of the following indications in the management of ALL: allo-SCT, RIC regimens for allo-SCT, TKIs following allo-SCT, and alternative donor transplants in the management patients who lack a suitable related or unrelated donor
> Published full-report articles of randomized control trials and non-randomized studies with an appropriate control group
> Studies reporting any of the outcomes of interest such as relapse, non-relapse mortality, disease-free survival, and overall survival

Exclusion Criteria

Studies were excluded if they were:

1. Abstracts, letters, case reports, comments, books, notes, or editorial publication types
2. Articles published in a language other than English because resources were not available for translation services

A review of the titles and abstracts that resulted from the search was conducted by one reviewer. For those items that warranted full text review, one reviewer reviewed each item and consulted members of the Working Group whenever there was uncertainty.

Refer to the "Results" section of the original guideline document for information on studies retrieved through the literature searches.

Number of Source Documents

Eight studies were included in the review (1 guideline, 3 systematic reviews, and 4 cohort studies).

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was conducted by one author and was reviewed by a second independent individual using a data audit procedure to verify the accuracy of the information obtained from the studies included in this report. All extracted data and information were reviewed independently by other members of the Working Group.

The following items were extracted from each relevant article: author, publication year, study design, sample size, procedure/intervention, number of participants, and years of data collection. Outcomes of interest including relapse, non-relapse mortality, disease-free survival, and overall survival were extracted when available.

Ratios, including hazard ratios (HRs), were expressed with a ratio <1.0 indicating that the intervention/experimental procedure had a better outcome than the control group.

Clinical trials were assessed for quality by examining the following seven criteria: the method of randomization, reporting of blinding, the power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, non-randomized and single-arm evidence would be assessed according to full reporting of the patient selection criteria, the interventions each patient received, all relevant outcomes, and the source of funding. All authors reviewed and discussed a draft of this report with the aim of assessing the quality of the evidence as a whole, without the use of a scoring system or cut-offs, according to the policy of the Program in Evidence-based Care (PEBC).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Recommendation Report Developers

This recommendation report was developed by a Working Group consisting of four haematologists/oncologists and a health research methodologist at the request of the Stem Cell Transplantation (SCT) Committee.

The Working Group was responsible for reviewing the evidence base, drafting the recommendations, and responding to comments received during the document review process.

Recommendation Report Development Methods

The Program in Evidence-based Care (PEBC) produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. For Recommendation Reports this process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by a methodology experts and final approval by the Sponsoring Committee.

The PEBC uses the Appraisal of Guidelines Research and Evaluation (AGREE II) framework as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook (see the "Availability of Companion Documents" field).

Research Questions

From the objectives, the following research questions were derived to direct the search for available evidence to inform recommendations to meet the objectives.

1. Does allogeneic stem cell transplantation (allo-SCT) improve the outcome of adult patients with acute lymphoblastic leukemia (ALL) in first complete remission (CR1) or beyond when compared with conventional chemotherapy (CT)?
2. Does a reduced-intensity conditioning (RIC) or non-myeloablative conditioning allo-SCT improve the outcome of adult patients with ALL who are not suitable for ablative regimens when compared with standard non-transplant therapies?
3. Does the use of BCR-ABL tyrosine kinase inhibitors (TKIs) following allogeneic transplantation improve the outcome of adult patients with Philadelphia chromosome-positive ALL when compared with allogeneic transplantation without TKI?
4. Does alternative donor transplant (haploidentical, cord blood) improve the outcome of adult patients with ALL who lack a suitable related

or unrelated donor compared with standard, non-transplant chemotherapy?

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Recommendation Report Review and Approval

Internal Review

The recommendation report was reviewed by the Director of the Program in Evidence-based Care (PEBC). The Working Group is responsible for ensuring the necessary changes are made. If those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

Report Approval by the Stem Cell Transplant Steering Committee

After internal review, the report was presented to the Cancer Care Ontario Stem Cell Transplantation (CCO-SCT) Steering Committee. Members of the CCO-SCT previously reviewed the document, and formally approved the document.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by a clinical guideline, systematic reviews with meta-analysis, and cohort studies.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- The guideline committee found evidence of some benefit of stem cell transplantation (SCT) in acute lymphoblastic leukemia (ALL) in first complete remission (CR1) based on two meta-analyses, one of which was an individual patient data meta-analysis. Both overall survival and disease-free survival was improved for patients receiving a SCT for ALL in CR1. The evidence was strongest in Philadelphia chromosome negative ALL in CR1.
- Two retrospective cohort studies compared the efficacy of haploidentical hematopoietic stem cell transplantation (haplo-SCT) with chemotherapy alone when used as post-remission treatment in patients with ALL. Both studies showed improvement in relapse rate, disease control and overall survival in favour of the haplo-SCT patients. Non-relapse mortality was at acceptable levels.

Potential Harms

Qualifying Statements

Qualifying Statements

- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.
- See the original guideline document for qualifying statements related to each recommendation.

Implementation of the Guideline

Description of Implementation Strategy

Implementation Considerations

Should an increase in stem cell transplantation (SCT) for acute lymphoblastic leukemia (ALL) result from this recommendation report, there may be issues related to capacity and timeliness of transplant in Ontario centres. Also, the use of haploidentical donors and reduced-intensity conditioning (RIC) could increase the number of patients with ALL who may become eligible for a SCT. Due to the nature of the evidence showing improved outcomes in terms of survival and disease control, SCT for ALL would align with patient and provider values.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

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treatment of acute lymphoblastic leukemia. Toronto (ON): Cancer Care Ontario (CCO); 2016 Feb 1. 37 p. (Program in Evidence-based Care (PEBC) Recommendation Report; no. SCT-6). [32 references]

Adaptation

Agreement with the recommendations contained in the American Society for Blood and Marrow Transplantation (ASBMT) guideline led to the Working Group members' decision to adapt its recommendations, with additional searching to be undertaken to ensure the currency of the evidence-base in the role of allogeneic stem cell transplantation (allo-SCT) for the management of acute lymphoblastic leukemia (ALL) in the adult population:

- Oliansky DM, Larson RA, Weisdorf D, Dillon H, Ratko TA, Wall D, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukemia: update of the 2006 evidence-based review. Biol Blood Marrow Transplant. 2012 January;18(1):18-36.e6.

Date Released

2016 Feb 1

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario (CCO) supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Stem Cell Transplantation Treatment for Acute Lymphoblastic Leukemia Working Group

Stem Cell Transplant Steering Committee

Composition of Group That Authored the Guideline

Working Group Members: Christopher Bredeson (*Working Group Chair*), Head, Malignant Hematology & Stem Cell Transplantation, Ottawa Hospital Research Institute and Department of Medicine, Ottawa, Ontario; Tom Kouroukis (*Hematology Disease Site Lead*), Division of Malignant Hematology, Juravinski Cancer Centre, Hamilton, Ontario; Irwin Walker, Director, Hamilton Bone Marrow Transplant Program, Director (Adults), Hamilton-Niagara Regional Hemophilia Program, Division of Hematology & Thromboembolism, Juravinski Cancer Centre, Hamilton, Ontario; John Kuruvilla, Hematologist, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Ontario; Norma Varela (*Health Research Methodologist*), Program in Evidence-based Care (PEBC), McMaster University, Hamilton, Ontario

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy [redacted], the guideline authors

of this recommendation report and internal reviewers were asked to disclose potential conflicts of interest. The authors, members, and reviewers reported that they had no conflicts of interest.

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Please visit the Cancer Care Ontario (CCO) Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Cancer Care Ontario (CCO) Web site.

Availability of Companion Documents

The following are available:

- Stem cell transplantation in the treatment of acute lymphoblastic leukemia. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2016 Feb 1. 6 p. Available from the Cancer Care Ontario (CCO) Web site.
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available from the CCO Web site.
- Program in Evidence-based Care methods handbook. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 23. Available from the Program in Evidence-based Care (PEBC) Toolkit Web site.
- Program in Evidence-based Care document assessment and review protocol. Toronto (ON): Cancer Care Ontario (CCO); 2015 Apr 16. 15 p. Available from the CCO Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 24, 2016.

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